

Thresholds?

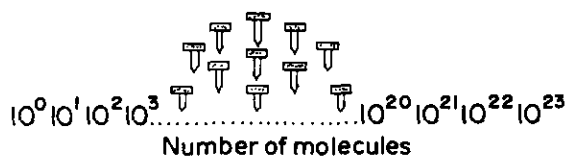
by David P. Rall*

Many diseases resulting from exposure to foreign chemicals are delayed in their onset and, to some extent at least, are irreversible. That is, if the chemical is removed, the disease continues to progress, or at least not regress. Typical are the diseases called cancer. Mutagenic effects, well documented in laboratory animals but extremely difficult to document in the human population, also fit into this category. Chronic liver, lung, and probably kidney and central nervous system diseases are also long-delayed and have an element of irreversibility about them.

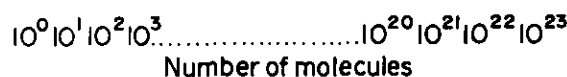
The critical problem involved is whether or not these chronic irreversible toxic effects are associated with a threshold. Is there a concentration of a toxic chemical compound which causes no ill effects in the population? If there is a threshold and if the threshold can be determined experimentally, then cost-benefit analyses are greatly simplified, because very often the environmental concentration can be held below the threshold.

Most scientists would agree that a highly potent carcinogen such as an aflatoxin, nitrosamine, or a chloromethyl ether is probably perfectly safe at an exposure level of one molecule, ten molecules, a hundred molecules, or maybe even a thousand molecules per mouse or rat or dog or man; but we all believe that it is totally unsafe to be exposed to 10^{20} , 10^{21} , 10^{22} , or 10^{23} molecules of this same compound (Fig. 1a). In an isolated situation in a clean laboratory experiment it is perfectly reasonable to expect that very low concentrations have such a low probability of causing a deleterious effect as to be essentially zero. In point of fact, we can never determine this. To design an experiment to show whether or not such a statement is correct would take enormous resources, and, even if the experiment could be performed, the answer would probably be suspect.

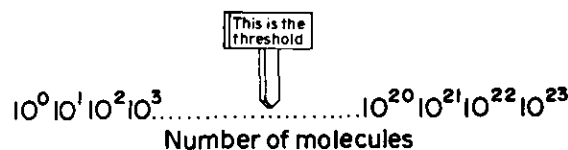
The problem really is where along this continuum from 10^0 up to 10^{23} molecules, do you put the little sign that says, "This is the threshold?" (Fig. 1b). I don't know where that sign should go, and I don't think anyone knows.



a



b



c

FIGURE 1. Thresholds for chemicals that cause chronic irreversible damage.

*National Institute of Environmental Health Sciences, National Institutes of Health Research Triangle Park, North Carolina 27709.

A more fruitful way to look at this is to ask the question: "A threshold for whom?" The human population in the United States, the population we are trying to protect, is a very large, diverse, genetically heterogeneous population, exposed to a variety of toxic agents. Genetic variability to carcinogenesis is well documented, and we are beginning to understand some of the causes of this variability. There is now evidence that the amount of an enzyme, arene oxidase, or aryl hydroxylase, which is genetically controlled, may determine the susceptibility to lung cancer from cigarette smoking. If you have a lot of the enzyme, you tend to be highly susceptible. If you have a little of the enzyme, you are not particularly susceptible. It is also well known that people who are deficient in immunological competence are particularly susceptible to cancer. Therefore, any condition—be it genetic or environmental—that affects immunologic competence, can also affect susceptibility to cancer. Individuals who are deficient in DNA repair processes also are more susceptible to cancer. This is demonstrated by studies of patients with xeroderma pigmentosa. Such persons are highly susceptible to ultraviolet induced skin cancer, and it can be demonstrated that they have deficient DNA repair.

It seems, therefore, that instead of one sign saying, "This is the threshold," we really need a whole series of little signs, a forest of signs, saying, "This is the threshold" for this person or this part of the population (Fig. 1c). The question then becomes: "Whose threshold and when?"

Another way of looking at the threshold problem is to consider the curve relating cancer mortality to the age of the population in the United States; in this instance it is for 1965 (Fig. 2). There is a smooth curve of increased mortality after the age 35, begin-

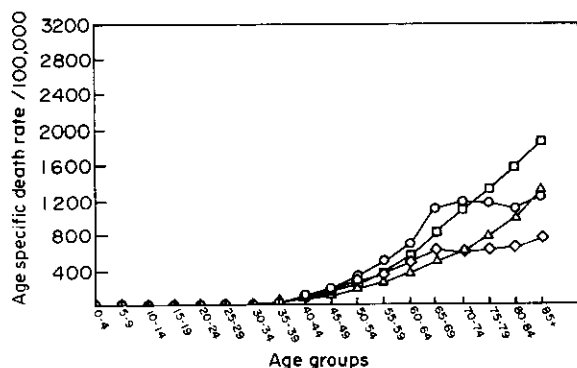


FIGURE 2. Age distribution of all malignant neoplasms: (□) male white; (○) male nonwhite; (△) female white; (◇) female nonwhite.

ning to become asymptotic after about age 65 in blacks, but not whites. This is the same sort of curve that an oncologist would see, had he administered a moderately strong carcinogen to a large group of experimental animals. In other words, it looks like a typical dose-response curve for a carcinogenic substance. This, of course, strongly suggests that we are all exposed to significant amounts of carcinogens. And we know that there are carcinogenic compounds in our environment. In most people these carcinogen concentrations are not high enough (or the individuals not susceptible enough) to cause cancer in their lifetime.

This I would propose as the added risk factor rather than the threshold-no threshold debate. I suggest added risk, but it can be argued that mixtures of two or more carcinogens are not only additive but can be synergistic. Indeed, there is some evidence that there can be actual antagonism between some carcinogenic substances, but the simple concept of an additive effect between existing carcinogens and a newly introduced one would be most likely. Since the U. S. population is exposed to cancer-producing agents, it seems logical that the addition of any amount of a carcinogen will increase the risk of the cancer appearing, or appearing earlier, and adversely affecting life. It is clear, to me at least, that adding carcinogens will increase the probability of death by cancer. It is also clear that this probability can be very low indeed—that if a very small amount of carcinogen is added, the increased probability—the added risk factor—will be in the order of one in a million, one in ten million per year. This, I think, underlines the important efforts to develop statistical models such as the Bryan-Mantel model or the linear model to provide an estimate of what the increased incidence of cancer might be with the addition of very small amounts of carcinogens.

But the issue is not thresholds or no thresholds; it is one of adding a new carcinogen to a pool of present carcinogens. I would suggest, therefore, that there may well be thresholds with carcinogenic substances when given to a very clean animal in an environmentally controlled situation, that is, when there are few or no other carcinogens present; this is what the experimental oncologist tries to create in the standard laboratory animal test system—a clean animal of known and homogeneous genetic background with a well characterized diet and no known carcinogens living in sterile filtered air. The human population is different, however: the mouse doesn't smoke or breathe hydrocarbons or sulfur oxides from fossil fuels, doesn't drink, doesn't take

medicine, doesn't eat bacon or smoked salmon, but man does.

The current controversy regarding the occurrence of thresholds for carcinogenic and mutagenic chemicals will in the normal course of scientific events be resolved as a scientific consensus, but this will take years to decades. In the meantime, judgments and regulatory decisions must be made on the basis of incomplete information.

One wonders however about the implications of

each of the two possible decisions that might turn out to be wrong.

If thresholds do exist and the regulatory decisions are based on a no-threshold concept, there will be short-term economic losses. If thresholds do not exist and the regulatory decisions are based on thresholds, then there will be fewer short-term economic losses, but we would face a future of damaged human somatic and germinal DNA and an increased incidence of neoplastic diseases.